The Metabolic Syndrome And Kidney

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What is Metabolic Syndrome

- A group of manifestations which when clustered together will increase the risk of cardiovascular events and development of type II diabetes
- Any three occurrences of the following criteria is considered positive for metabolic syndrome
  1. Central obesity
  2. High BP
  3. Insulin Resistance
  4. High serum triglycerides
  5. Low HDL Cholesterol

Impact

- Weather a syndrome or **simply a cluster of risk factors**, these individuals are more prone to:
  - Cardiovascular disease
  - Type II Diabetes
- The metabolic syndrome is:
  - Pro-thrombotic
  - Pro-inflammatory

More complications develop when +ve patients develop CVS disease or diabetes than those without metabolic syndrome criteria

History

- First official description as a syndrome by Reaven from Stanford University in 1988
- However, much earlier reports have described the very common coexistence of the various components of the syndrome

Other Names For Metabolic Syndrome

Diagnosis of Metabolic Syndrome

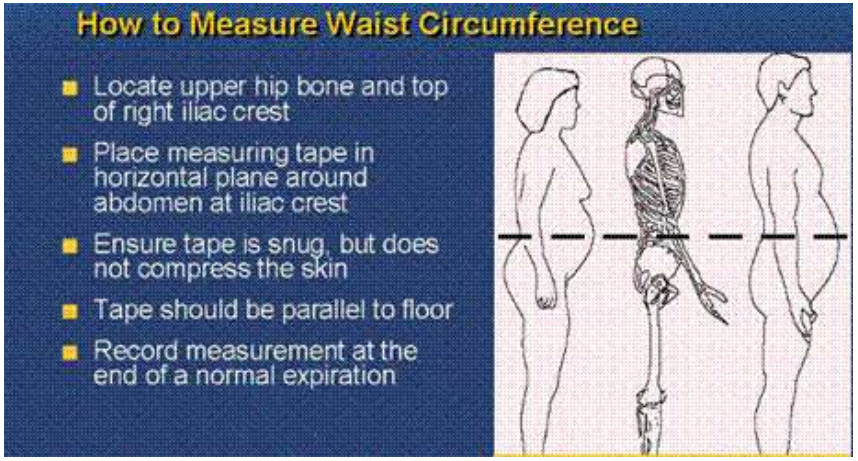
- Three or more of the these five criteria should be present
  1. Central obesity
  2. High BP
  3. Insulin Resistance
  4. High serum triglycerides
  5. Low HDL Cholesterol
- Many current definitions are present with different “cut off” values

Insulin Resistance

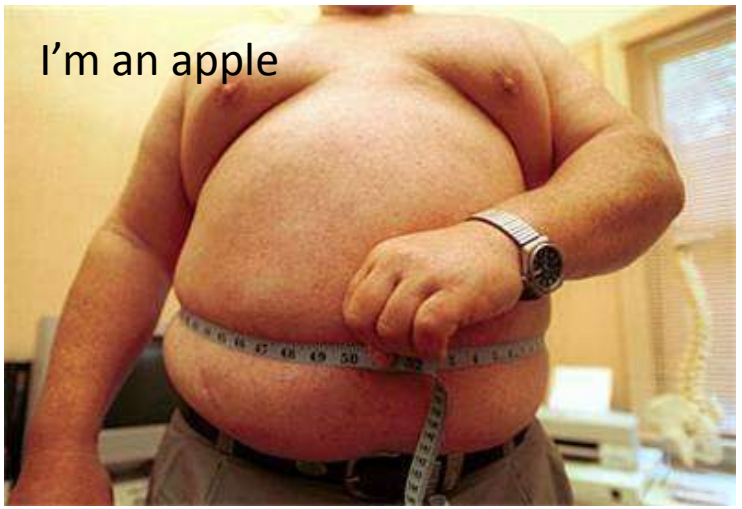
- FBS =/>110
- and/or pp =/> 140
- or diagnosed Diabetes
- or fasting hyperinsulinemia

Central Obesity

- The presence of Obesity may precede the development of other metabolic syndrome components
- To diagnose central obesity
- Waist Circumference
  - =/> 102 cm (men)
  - =/> 88 cm (women)
- Waist to hip ratio
  - >0.9 (men)
  - >0.85 (women)



I’d Rather Be a Pear Than An Apple



Hypertension

- =/> 140/90 mmHg
- or drug treatment for hypertension

Dyslipidemia

- Low HDL Cholesterol
  - <40 mg/dL (men);
  - < 50 mg/dL (women)
  - or drug treatment for low HDL-C
- Hypertriglyceridemia
  - =/> 150 mg/dL (1.7 mmol/L)
  - or drug treatment for elevated triglycerides

Other Factors of the Metabolic Syndrome

- They may be not included in criteria, but they are important “music players” in the “symphony of death”
  - postmenopausal status,
  - smoking,
  - low household income,
  - high carbohydrate diet
  - physical inactivity
  - Use of atypical antipsychotic medications, especially clozapine
- poor cardiorespiratory fitness is an independent and strong predictor of metabolic syndrome in both men and women!!!

Pathogenesis

- Multiple and Complex contributing factors
  - Insulin Resistance
  - Obesity
  - Dyslipidemia
  - Glucose intolerance
  - Hypertension
  - Increased Inflammatory Cytokines

Insulin Resistance

- Expanded Adipose tissue ⇨ ↑ FFA ⇨ inhibiting insulin-mediated glucose uptake ⇨ Insulin rsistanc
  - IR ⇨ hyperglycemia ⇨ hyperinsulinemia
- Hyperinsulinemia, will prevent fatty acid oxidation ⇨ ↑ FFA
- Also, increased Free Fatty Acids ⇨ ↑ triglycerides and ↑ secretion of VLDL

Metabolically Obese With Normal Weight

- typically having increased amount of visceral adipose tissue
- Theoretically, a higher rate of flux of adipose tissue-derived free fatty acids to the liver through the splanchnic circulation would be expected

Dyslipidemia

- Increased Fatty acids influx into liver ⇨
  - increased synthesis of VLDL to carry them!!
  - Incorporation of FFA to form triglycerides by the liver
- Due to increased triglycerides, there is a change in HDL composition and metabolism
  - Resulting in ↓ cholesterol content of HDL

Glucose Intolerance

- Insulin Resistance ⇨
  - Failure to suppress gluconeogenesis in the liver
  - Failure mediate glucose uptake in insulin sensitive tissues (i.e. muscle and adiposetissue).
- To compensate ↑↑ insulin secretion
  - If this compensation fails, hyperglycaemia occurs.
- FFA ⇨ stimulate insulin secretion,
  - BUT!!!prolonged exposure to excessive concentrations of FFA results in falls in insulin secretion.
  - The mechanism for this alteration has been attributed to lipotoxicity.

Hypertension

- A very well established connection between Hyperinsulinemia and Hypertension
  - Salt retention by the kidney
  - Increased sympathetic nervous system activity
  - Anabolic effect of insulin and its growth factors

Inflammatory Cytokines and the Metabolic Syndrome

- The Metabolic Syndrome is
  - pro-inflammatory
  - pro-thrombotic
- It is associated with increased levels of
  - **C-reactive protein**
  - IL-6
  - plasminogen activator inhibitor


SO SIMPLE!!!

Metabolic Syndrome In Egypt

- From Nutrition National Institute:
  - A prevalence of about 7.4% in young age of 10-18 years
    - Nebal abo ElEla et al., Journal of Clinical Lipidology Volume 4, Issue 3 , Pages 185-195, May 2010
- Another report from Suez Canal University
  - An incidence of 28.0% of men and 34.0% of women in a Survey of 773 adults around the age of 40
    - Hamdy Selim Et al., Indian J Endocrinol Metabv.16(1); Jan-Feb 2012

METABOLIC SYNDROME AND THE KIDNEY

Metabolic Syndrome and Development of Proteinuria

- Patients with metabolic syndrome develop more About 800 African Americans with CKD (GFR<60) were evaluated
  - Those fitting at least 3 criteria for metabolic syndrome were found to have greater levels of proteinuria.
    - Lea et al., Am J Kidney Dis 51:732-740. © 2008

Metabolic Syndrome and Development of Kidney Disease

- Around 15,000 patients with CKD (GFR<60 and/or microalbuninuria) were analysed.
  - The ratio of patients with at least 3 parameters of metabolic syndrome to those without evidence of metabolic syndrome was 2.6:1.89
    - Chen et al., Nephrol Dial Transplant (2007) 22: 1100–1106
- A similar study involving 10,000 patients showed similar results
    - Kurella et al., J Am Soc Nephrol 16: 2134 –2140, 2005
- Another Japanese study involving 6,000 patients brought up the same observation
    - Tozawa et al., *Hypertension Research* (2007) **30,** 937–943

Therefore

- ***The metabolic syndrome is independently associated with an increased risk for incident CKD in non-diabetic adults.***
- ***Thus,*** **Detection and treatment of metabolic syndrome should be stressed as a strategy to prevent CKD**

Mechanism Of Metabolic Syndrome and CKD

- Obesity and insulin resistance have been associated with secretion of inflammatory mediators and activation of inflammation associated signaling pathways
  - It seems macrophages that infiltrate fat tissue, is the principal site of obesity related cytokine synthesis
  - leptin, IL-6, TNF-, adiponectin, and acylation-stimulating protein
  - many of these cytokines have been suggested to mediate renal disease pathophysiology
  - Therefore, it is speculated that progressive kidney disease could be regulated by proinflammatory cytokines in the context of the metabolic syndrome.
- Other factors include physical compression of kidney parenchyma by adipose tissue, sleep apnea, reduced nephron number, enhanced glucocorticoid activity, or altered uric acid metabolism

Metabolic Syndrome and CKD Progression

- Due to its complex inter-relations, it is difficult to identify metabolic syndrome as an independent factor for CKD progression due to presence of:
  - Proteinuria, diabetes and hypertension
  - Which are major factors for CKD progression
  - And overlap with the metabolic syndrome
- Lea et al., by following the patients failed to prove a direct relation between metabolic syndrome and CKD progression
  - However there is a strong relationship between metabolic syndrome and the degree of proteinuria compared with non metabolic syndrome patients
  - And proteinuria is a major CKD progression factor!!
    - Lea et al., Am J Kidney Dis 51:732-740. © 2008

Metabolic Syndrome and CKD Progression

- It is therefore justified to manage metabolic syndrome to slow CKD progression by
  - Controlling obesity and losing weight
  - Correcting hyperlipidemia
- However, Metabolic syndrome loses its predictive power in late-stage chronic kidney disease progression
  - Lea et al., Clin Nephrol. 2011 Feb;75(2):141-9.

Metabolic Syndrome and Dialysis

- Based on reverse epidemiology in dialysis:
  - Flesh weight gain is a marker of better quality of life and better survival on maintenance hemodialysis
  - Hypercholesterolemia is one sign of good nutritional index
- The only significant criteria for CVS events (CVEs) in chronic hemodialysis was the **waist circumference**
- Otherwise there was no difference in CVEs, hospitalizations or deaths between patients with and without Metabolic syndrome
  - Chia-Chun Wu et al., Nephrol Dial Transplant (2011) 26: 3689–3695 (From Taiwan)

Therapeutic Strategies

- Rationale
  - **Detection and treatment of metabolic syndrome should be stressed as a strategy to prevent CKD**
  - A major contributor to slowing of progression of CKD is management of metabolic syndrome
  - Although not enough long term studies are available on the effects of treatment of metabolic syndrome on CKD incidence and progression, it is justified to treat
    - To prevent cardiovascular, diabetic, and thrombotic complications in CKD patients

Multiple Discipline Approach

Therapeutic Lifestyle Changes (TLC)	Hyperglycaemia / Insulin Resistance	Hypertension	Atherogenic Dyslipidaemia	Antiplatelet therapy
– Reduce weight – Diet: 'Mediterranean', rich in un-(mono-) saturated fats, fiber, complex carbohydrates – Increase physical activity – Quit smoking	– Weight reduction – Drug treatment?*	– TLC – Reduce salt intake – Drug treatment (especially ACE inhibitors, and ARBs)	– TLC – Plant sterols/stanols – Drug treatment (especially statins)	–Low dose aspirin (for high CVD risk subjects)

Do you think I have metabolic syndrome?!!